1.4.1. Prescribing Information (Summary of Products Characteristics)

1. Name of the Finished Pharmaceutical Product

Verbital 50 (Phenobarbital Tablet BP 50mg)

2. Qualitative and Quantitative composition

2.1 Qualitative composition

Each uncoated tablet contain

Phenobarbital BP…….50 mg

Excipients……..q.s.

2.2 Quantitative composition

Each uncoated tablet contain

Phenobarbital BP…….50 mg

Excipients……..q.s.

2.3 Salts and hydrates

NA

2.4 Esters and pro-drugs

Not Applicable

2.5 Oral powders for solution or suspension

Not Applicable

2.6 Parenterals excluding powders for reconstitution

NA

2.7 Powders for reconstitution prior to parenteral administration

Not Applicable

2.8 Concentrates

Not Applicable

2.9 Transdermal patches

Not Applicable

2.10 Multi dose solid or semi-solid products

Not Applicable

2.11 Biological medicinal products

2.11.1 Expression of strength

Not Applicable

2.11.2 The biological origin of the active substance

Not Applicable

2.11.3 Special provisions for normal immunoglobulins

Not Applicable

2.11.4 Herbal pharmaceutical products

Not Applicable

3. Pharmaceutical form

Uncoated Tablet

4. Clinical particulars

4.1 Therapeutic indications

1) Phenobarbital is recommended for all forms of epilepsy (except absence seizures).

4.2 Posology and method of administration

Adults: 60-180mg at night

Child: 5-8mg/kg daily

Elderly: Phenobarbital clearance diminishes in the elderly. Therefore the dose of phenobarbital is usually lower in elderly patients.

The dose of Phenobarbital should be adjusted to meet the needs of individual patients. This usually requires plasma concentration of 15 to 40 micrograms/ml (65 to 170 micromoles/litre).

4.3 Method of Administration

For oral administration

4.4 Contraindications

Phenobarbital should not be given to patients with:

• Known hypersensitivity to phenobarbital, other barbiturates or other ingredients in the tablet

• Acute intermittent porphyia

• Severe respiratory depression

• Severe renal or hepatic impairment.

4.5 Special warnings and precautions for use

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for phenobarbital.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Steven-Johnson syndrome and toxic epidermal necrolysis

Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of phenobarbital. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment.

If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, Phenobarbital treatment should be discontinued. The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of phenobarbital, phenobarbital must not be re-started in this patient at any time.

Women of childbearing potential

Phenobarbital may cause foetal harm when administered to a pregnant woman. Prenatal exposure to phenobarbital may increase the risk for congenital malformations approximately 2- to 3-fold (see section 4.6).

Phenobarbital should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options.

Women of childbearing potential should be fully informed of the potential risk to the foetus if they take phenobarbital during pregnancy.

A pregnancy test to rule out pregnancy should be considered prior to commencing treatment with phenobarbital in women of childbearing potential.

Women of childbearing potential should use highly effective contraception during treatment and for 2 months after the last dose. Due to enzyme induction, phenobarbital may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use other contraceptive methods (see sections 4.5 and 4.6).

Women planning a pregnancy should be advised to consult in advance with her physician so that adequate counselling can be provided and appropriate other treatment options can be discussed prior to conception and before contraception is discontinued.

Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant while on treatment with phenobarbital.

Care should be used in the following situations:

• Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine

• Respiratory depression (avoid if severe)

• Young, debilitated or senile patients

• Renal impairment

• Existing liver disease

• Sudden withdrawal should be avoided as severe withdrawal syndrome (rebound insomnia, anxiety, tremor, dizziness, nausea, fits and delirium) may be precipitated

• Acute chronic pain – paradoxical excitement may be induced or important symptoms masked.

• Prolonged use may result in dependence of the alcohol-barbiturate type. Care should be taken in treating patients with a history of drug abuse or alcoholism.

4.6 Interaction with other medicinal products and other forms of interaction

Effects on Phenobarbital	Effects of Phenobarbital on other medicines
• Alcohol – concurrent administration with alcohol may lead to an additive CNS depressant effect. This is likely with concurrent administration with other CNS depressants. • Antidepressants – including MAOIs, SSRIs and tricyclics may antagonise the antiepileptic activity of phenobarbital by lowering the convulsive threshold • Antiepileptics - phenobarbital plasma concentrations increased by oxcarbazepine, phenytoin and sodium valproate. Patients treated concomitantly with valproate and phenobarbital should be monitored for signs of hyperammonemia. In half of the reported cases hyperammonaemia was asymptomatic and does not necessarily result in clinical encephalopathy. Vigabatrin possibly decreases phenobarbital plasma concentrations. • Antipsychotics – concurrent use of chlorpromazine and thioridazine with phenobarbital can reduce the serum levels of either drug. • Folic acid – if folic acid supplements are given to treat folate deficiency, which can be caused by the use of phenobarbital, the serum phenobarbital levels may fall, leading to decreased seizure control in some patients. (see section 4.6). • Memantine – the effect of Phenobarbital is	Phenobarbital increases the rate of metabolism reducing serum concentrations of the following drugs: • Anti-arrhythmics – disopyramide and quinidine loss of arrhythmia control is possible. Plasma levels of antiarrhymics should be monitored, if phenobarbital is added or withdrawn. Changes in dosage may be necessary. • Antibacterials – chloramphenicol, doxycycline, metronidazole and rifampicin. Avoid concomitant use of telithromycin during and for 2 weeks after Phenobarbital. • Anticoagulants. • Antidepressants – paroxetine, mianserin and tricyclic antidepressants. • Antiepileptics – carbamazepine, lamotrigine, tiagabine, zonisamide, primidone and possibly ethosuxamide. • Antifungals – the antifungal effects of griseofulvin can be reduced or even abolished by concurrent use. Phenobarbital possibly reduces plasma concentrations of itraconazole or posaconazole. Avoid concomitant use of voriconazole. • Antipsychotics – phenobarbital possibly reduces concentration of aripiprazole. • Antivirals – phenobarbital possibly reduces plasma levels of abacavir, amprenavir, darunavir, lopinavir, indinavir, nelfinavir, saquinavir. • Anxiolytics and Hypnotics – clonazepam.

possibly reduced. • Methylphenidate – plasma concentration of Phenobarbital is possibly increased. • St John's wort (*Hypericum perforatum*) – the effect of phenobarbital can be reduced by concomitant use of the herbal remedy St John's wort.	• Aprepitant – phenobarbital possibly reduces plasma concentration of aprepitant. • Beta-blockers – metoprolol, timolol and possibly propranolol. • Calcium channel blockers – phenobarbital causes reduced levels of felodipine, isradipine, diltiazem, verapamil, nimodipine and nifedipine and an increase in dosage may be required. • Cardiac Glycosides – blood levels of digitoxin can be halved by concurrent use. • Ciclosporin or tacrolimus. • Corticosteroids. • Cytotoxics – phenobarbital possibly reduces the plasma levels of etoposide or irinotecan. • Diuretics – concomitant use with eplerenone should be avoided. • Haloperidol- serum levels are approximately halved by concurrent used with phenobarbital. • Hormone Antagonists – gestrinone and possibly toremifene. • Methadone – levels can be reduced by concurrent use of phenobarbital and withdrawal symptoms have been reported in patients maintained on methadone when phenobarbital has been added. Increases in the methadone dosage may be necessary. • Montelukast. • Oestrogens – reduced contraceptive effect. • Progestogens – reduced contraceptive effect. • Sodium oxybate – enhanced effects, avoid concomitant use. • Theophylline – may require an increase in

	theophylline dose. • Thyroid hormones-may increase requirements for thyroid hormones in hypothyroidism. • Tibolone • Tropisetron • Vitamins – barbiturates possibly increase requirements for vitamin D

Phenobarbital may interfere with some laboratory tests including metyrapone test, phenlolamine tests and serum bilirubin estimation.

4.7 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Phenobarbital should not be used in women of childbearing potential unless the potential benefit is judged to outweigh the risks following careful consideration of alternative suitable treatment options.

A pregnancy test to rule out pregnancy should be considered prior to commencing treatment with phenobarbital in women of childbearing potential.

Women of childbearing potential should use highly effective contraception during treatment with phenobarbital and for 2 months after the last dose. Due to enzyme induction, phenobarbital may result in a failure of the therapeutic effect of oral contraceptive drugs containing oestrogen and/or progesterone. Women of childbearing potential should be advised to use other contraceptive methods while on treatment with phenobarbital, e.g. two complementary forms of contraception including a barrier method, oral contraceptive containing higher doses of estrogen, or a non-hormonal intrauterine device (see section 4.5).

Women of childbearing potential should be informed of and understand the risk of potential harm to the foetus associated with phenobarbital use during pregnancy and the importance of planning a pregnancy.

Women planning a pregnancy should be advised to consult in advance with her physician so that specialist medical advice can be provided and appropriate other treatment options can be discussed prior to conception and before contraception is discontinued.

Antiepileptic treatment should be reviewed regularly and especially when a woman is planning to become pregnant.

Women of childbearing potential should be counselled to contact her doctor immediately if she becomes pregnant or thinks she may be pregnant while on treatment with phenobarbital.

4.8 Pregnancy

Risk related to antiepileptic medicinal products in general

Specialist medical advice regarding the potential risks to a foetus caused by both seizures and antiepileptic treatment should be given to all women of childbearing potential taking antiepileptic treatment, and especially to women planning pregnancy and women who are pregnant.

Sudden discontinuation of antiepileptic drug (AED) therapy should be avoided as this may lead to seizures that could have serious consequences for the woman and the unborn child.

Monotherapy is preferred for treating epilepsy in pregnancy whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated AEDs.

Pregnancy

Risks related to phenobarbital

Phenobarbital crosses the placenta. Animal studies (literature data) have shown reproductive toxicity in rodents (see section 5.3).

Data from meta-analysis and observational studies showed a risk of major malformations about 2 to 3 times higher than the baseline risk of major malformations in the general population (which is 2-3%). The risk is dose-dependent; however, no dose has been found to be without risk. Phenobarbital monotherapy is associated with an increased risk of major congenital malformations, including cleft lip and palate and cardiovascular malformations. Other malformations involving various body systems including cases of hypospadias, facial dysmorphic features, neural tube effects, craniofacial dysmorphia (microcephaly) and digital abnormalities have also been reported.

Data from a registry study suggest an increase in the risk of infants born small for gestational age or with reduced body length, compared to lamotrigine monotherapy.

Neurodevelopmental disorders have been reported among children exposed to phenobarbital during pregnancy. Studies related to the risk of neurodevelopmental disorders in children exposed to phenobarbital during pregnancy are contradictory and a risk cannot be excluded. Pre-clinical studies have also reported adverse neurodevelopment effects (see section 5.3).

Phenobarbital should not be used during pregnancy unless the potential benefit is judged to outweigh the risks following consideration of other suitable treatment options.

If, following re-evaluation of treatment with phenobarbital, no other treatment option is suitable, the lowest effective dose of phenobarbital should be used. The woman should be fully informed of and understand the risks related to the use of phenobarbital during pregnancy.

When used in the third trimester of pregnancy, withdrawal symptoms may occur in the neonate, including sedation, hypotonia and sucking disorder.

Patients taking phenobarbital should be adequately supplemented with folic acid before conception and during pregnancy.

Folic acid supplementation during pregnancy can help to reduce the risk of neural defects to the infant.

Haemorrhage at birth and addiction are also a risk. Prophylactic treatment with vitamin K^1 for the mother before delivery (as well as the neonate) is recommended, the neonate should be monitored for signs of bleeding.

Breast-feeding

Phenobarbital is excreted into breast milk and there is a small risk of neonatal sedation. Breast-feeding is therefore not advisable.

4.9 Effects on ability to drive and use machines

Phenobarbital may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Patients should be advised to make sure they are not affected before undertaking any potentially hazardous tasks.

4.10 Undesirable effects

• *Blood and the lymphatic system disorders:* megaloblastic anaemia (due to folate deficiency), agranulocytosis, thrombocytopenia.

• *Musculoskeletal and connective tissue disorders:* Dupuytren's contracture, frozen shoulder, arthralgia, osteomalacia, rickets.

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with phenobarbital. The mechanism by which phenobarbital affects bone metabolism has not been identified.

• *Reproductive and breast disorders:* Peyronie's disease.

• *Psychiatric disorders:* paradoxical reaction (unusual excitement), hallucinations, restlessness and confusion in the elderly, mental depression, memory and cognitive impairment, drowsiness, lethargy.

• *Nervous system disorders:* hyperactivity, behavioural disturbances in children, ataxia, nystagmus.

• *Cardiac disorders:* hypotension.

• *Respiratory disorders:* respiratory depression.

• *Hepato-bilary:* hepatitis, cholestasis.

• *Skin and subcutaneous tissue disorders:* allergic skin reactions (maculopapular morbilliform or scarlatiniform rashes), other skin reactions such as exfoliative dermatitis, erythema multiforme.

Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4).

Frequency: very rare

• *General disorders and administration site conditions:* antiepileptic hypersensitivity syndrome (features include fever, rash, lymphadenopathy, lymphocytosis, eosinophilia, haematological abnormalities, hepatic and other organ involvement including renal and pulmonary systems which may become life threatening).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.11 Overdose

Toxicity varies between patients; tolerance will develop with chronic use. Features of poisoning are to be expected after ingestion of 1g in adults.

Features:

Drowsiness, dysarthria, ataxia, nystagmus and disinhibition. There may also be coma, cardiovascular collapse, cardiac arrest, hypotension, hypotonia, hyporeflexia, hypothermia, hypotension and respiratory depression.

Barbiturates decrease gut motility, which may lead to slow onset and worsening of symptoms or cyclical improvement and worsening of symptoms.

Management:

Consider activated charcoal (50g for an adult, 10-15g for a child under 5 years) if more than 10mg/kg body weight of phenobarbital has been ingested within 1 hour, provided the airway can be protected. Repeat dose activated charcoal is the best method of enhancing elimination of phenobarbital in symptomatic patients. In severe hypotension dopamine or dobutamine can be used. Treat rhabdomyolysis with urinary alkalinistion. Haemodialysis or haemofiltration may be required for cases of acute renal or severe hyperkalaemia.

Charcoal haemoperfusion is the treatment of choice for the majority of patients with severe barbiturate poisoning who fail to improve, or who deteriorate despite good supportive care.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC CODE: N03A A02

Phenobarbital is a long-acting barbiturate, which because of its depressant effect on the motor cortex, is used in the treatment of epilepsy.

Phenobarbital has a widespread depressant action on cerebral function. It has sedative effects and has some protective action against all varieties of human partial and generalised epilepsy, with the exception of absence seizures. Phenobarbital is also effective in preventing seizures in the corresponding experimental animal models of epilepsy. In different studies phenobarbital appears to have had inconsistent effects in suppressing experimental epileptic foci, and epileptic after-discharges, but it inhibits synaptic transmission, at least in the spinal cord. The drug's probable biochemical mechanism of action is through prolonging the opening time of Cl^- ion channels in postsynaptic neuronal membranes. This effect causes membrane hyperpolarisation and thus impairs nerve impulse propagation. Phenobarbital also decreases intraneuronal Na^+ concentrations, and inhibits Ca^{2+} influx into depolarised synaptosomes. It raises brain serotonin levels, and inhibits noradrenaline (norepinephrine) reuptake into synaptosomes. These additional biochemical actions may contribute towards the anticonvulsant effects of the drug.

5.2 Pharmacokinetic properties

Absorption – phenobarbital is readily absorbed from the gastrointestinal tract, although it is relatively lipid – insoluble; peak concentrations are reached in about 2 hours after oral administration.

Distribution – phenobarbital is about 45 to 60% bound to plasma proteins. Phenobarbital crosses the placental barrier and is distributed into breast milk.

Metabolism – the plasma half life is about 75 to 120 hours in adults but is greatly prolonged in neonates, and shorter (about 21 to 75 hours) in children. There is considerable interindividual variation in phenobarbital kinetics. Phenobarbital in only partly metabolised in the liver.

Elimination – about 25% of a dose is excreted in the urine unchanged at normal urinary pH.

5.3 Preclinical safety data

Published studies reported teratogenic effects (morphological defects) in rodents exposed to phenobarbital. Cleft palate is reported consistently in all preclinical studies but other malformations are also reported (e.g. umbilical hernia, spina bifida, exencephaly, exomphalos plus fused ribs) in single studies or species.

In addition, although data from the published studies are inconsistent, phenobarbital given to rats/mice during gestation or early postnatal period was associated with adverse

neurodevelopment effects, including alterations in locomotor activity, cognition and learning patterns.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose Monohydrate BP, magnesium stearate, Maize starch, Micro Crystalline Cellulose BP, P.V.P.K-30 BP, Purified Talc, Colloidal Anhydrous Silica & Sodium Starch Glycolate BP

6.2 Incompatibilities

Incompatible with macrogol.

6.3 Shelf life

Shelf-life

Three years from the date of manufacture.

Shelf-life after dilution/reconstitution

Not applicable.

Shelf-life after first opening

Not applicable.

6.4 Special precautions for storage

Store at a temperature not exceeding 30°C, protect from light and mosture.

6.5 Nature and contents of container

Each Alu/PVC blister contain 10 tablets, such 10 blisters are packed in a carton.

6.6 Special precautions for disposal and other handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorisation Holder

Verve Human Care Laboratories

15-A, Pharmacity,

Selaqui, Dehradun-248011

India

8. MARKETING AUTHORISATION NUMBER

Not Applicable

9. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION

Not Applicable

10. DATE OF REVISION OF THE TEXT

11. DOSIMETRY (IF APPLICABLE)

Not Applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

Not Applicable